

ASSESSMENT OF HAEMOPHILIC ARTHROPATHY IN PATIENTS WITH SEVERE HEMOPHILIA USING THE HEMOPHILIA EARLY ARTHROPATHY DETECTION WITH ULTRASOUND (HEAD-US) SCORE AND THE HEMOPHILIA JOINT HEALTH SCORE (HJHS) BY DIFFERENT CAREGIVERS

Ağır Hemofili Hastalarında Hemofilik Artropatinin Ultrasonla Hemofili Erken Artropati Tespiti (HEAD-US) Skoru ve Hemofili Eklem Sağlığı Skoru (HJHS) Kullanılarak Farklı Kullanıcılar Tarafından Değerlendirilmesi

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ABSTRACT

Objective: There are few studies on the assessment of hemophilic arthropathy using the hemophilia early arthropathy detection with ultrasound (HEAD-US) and hemophilia joint health score (HJHS) scores. This study aimed to examine how radiologists and rheumatologists could evaluate hemophilic arthropathy in individuals with severe hemophilia using HEAD-US and HJHS scores simultaneously.

Material and Methods: Between 2021 and 2022, 168 joints from 28 individuals with severe hemophilia A and B were investigated at six-month intervals (TP1 and TP2). The HJHS scores of all patients were recorded. The HEAD-US in each hemophilic patient's six joints (elbow, knee, and ankle) were evaluated by radiologists and rheumatologists.

Results: The ankle assessment by HEAD-US showed the highest rate (34%) of synovitis by radiologist evaluation at TP1 in patients with an HJHS score of 0. The knee assessment by HEAD-US showed the highest rate (56%) of synovitis and bone damage by rheumatologist evaluation at TP1 in patients with an HJHS score of 0. HEAD-US ankle and knee examinations revealed the highest rate of synovitis (34%) by radiologist evaluation at TP2 in patients with an HJHS score of 0. The HEAD-US knee assessment revealed the highest rate of synovitis (44%) by rheumatologist evaluation at TP2 in patients with an HJHS score of 0. In the assessment of elbow and knee joints, there was a moderate to good correlation between HJHS and HEAD-US scores by different caregivers at different time points ($p < 0.05$).

Conclusion: Our findings indicate that clinicians play a crucial role in the early diagnosis of subclinical hemophilic arthropathy, with HEAD-US scoring conducted by rheumatologists similar to radiologists in severe hemophilia patients without pathology in HJHS scoring.

Keywords: HEAD-US, HJHS, radiologist, rheumatologist

ÖZ

Amaç: Hemofilik artropatinin ultrasonla hemofili erken artropati tespiti (HEAD-US) ve hemofili eklem sağlığı (HJHS) skorları kullanılarak değerlendirilmesine ilişkin az sayıda çalışma vardır. Bu çalışmanın amacı ağır hemofili hastalarında hemofilik artropatinin HEAD-US ve HJHS skorları kullanılarak radyolog ve romatologlar tarafından eş zamanlı değerlendirilmesini karşılamaktır.

Gereç ve Yöntemler: Altı aylık aralıklarla, ağır hemofili A ve B'li 28 hastanın 168 eklemi 2021 ve 2022 yılları arasında iki farklı zaman noktasında (TP1 ve TP2) incelendi. Tüm hastaların HJHS skorları kaydedildi. Her hemofilik hastanın altı eklemindeki (dirsek, diz ve ayak bileği) HEAD-US skorları radyologlar ve romatologlar tarafından değerlendirildi.

Bulgular: HEAD-US ile yapılan ayak bileği değerlendirmesi, HJHS skoru 0 olan hastalarda TP1'de en yüksek sinovit oranı (%34) radyolog değerlendirmesi ile saptandı. HEAD-US ile yapılan diz değerlendirmesi, HJHS skoru 0 olan hastalarda TP1'de en yüksek sinovit ve kemik hasarı oranı (%56) romatolog değerlendirmesi ile bulundu. HEAD-US ayak bileği ve diz muayenesinde, HJHS skoru 0 olan hastalarda TP2'de en yüksek sinovit oranı (%34) radyolog değerlendirmesi ile tespit edildi. HEAD-US diz değerlendirmesi, HJHS skoru 0 olan hastalarda TP2'de en yüksek sinovit oranı (%44) romatolog değerlendirmesi ile saptandı. Dirsek ve diz eklemlerinin değerlendirilmesinde HJHS ile HEAD-US arasında orta ile iyi derece korelasyon tespit edildi ($p < 0.05$).

Sonuç: Bulgularımız HJHS skorlamada patoloji saptanmayan ağır hemofili hastalarında radyologlara benzer şekilde romatologlar tarafından yapılan HEAD-US skorlama ile subklinik hemofilik artropatinin erken teşhisinde klinisyenlerin de önemli rolü olduğunu göstermektedir.

Anahtar Kelimeler: HEAD-US, HJHS, radyolog, romatolog



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INTRODUCTION

Early detection and treatment of hemophilic arthropathy are critical for preventing permanent joint disability in hemophilia patients. For many years, the hemophilia joint health score (HJHS) and the Petterson score on direct graphy have been used to assess hemophilic arthropathy (1,2). Furthermore, magnetic resonance imaging (MRI) is still the gold standard method for assessing subclinical hemophilic arthropathy in these patients, but it is also time-consuming and expensive (3). However, the new radiological method has improved the detection of hemophilic early arthropathy using the HEAD-US (hemophilia early arthropathy detection with ultrasound) score (4). A few studies on the assessment of hemophilic arthropathy using HEAD-US and HJHS scores have been reported (5,6). Otherwise, it is well known that the rheumatologist has been trained in musculoskeletal ultrasonography in rheumatoid arthritis patients through an EULAR course for years (7). To our knowledge, no rheumatologists have investigated hemophilic arthropathy in patients with hemophilia using HEAD-US.

To address this gap in the field, our study aimed to compare and correlate HJHS and HEAD-US scores in patients with severe hemophilia by different caregivers.

MATERIALS AND METHODS

This prospective longitudinal cohort study was conducted at Gazi University's Pediatric Hematology Unit in Türkiye from 2021 to 2022, after ethical permission. The ethics committee approved the study with decision number 479 on July 13, 2020. Informed consent was obtained from all patients and their parents.

Study population

Thirty patients with severe hemophilia were enrolled. One patient had a radiosynovectomy, and the other had a prosthesis, thus they were both excluded. Patients with mild to moderate hemophilia or von Willebrand disease were ruled out from the study.

In 28 patients with severe hemophilia, 168 joints were investigated. All of them received factor prophylaxis. There were 23 patients with severe hemophilia A [FVIII<1%], and 5 with severe hemophilia B [FIX<1%]. The following patient information was obtained: prophylaxis type, inhibitor status, target joint, and HJHS score.

Study design

The joint health status was assessed simultaneously by HJHS and HEAD-US for a total of 28 consecutive patients at two different time points: the first at the start of the study [time point TP1], and the second six months later [TP2]. HEAD-US and HJHS scores were utilized at the same appointment to assess hemophilic arthropathy in target joints (elbows, knees, and ankles) in individuals over the age of six. Different caregivers (radiologists and rheumatologists) evaluated the HEAD-US in each hemophilic patient's six joints (Figure 1). The order of the HEAD-US examination was assigned at random to each patient, and the blinded HEAD-US scores were calculated at two different time points by either a radiologist or a rheumatologist. The EULAR training for rheumatologists awarded a musculoskeletal US certificate. All readers had received at least two days of HEAD-US training from a qualified radiologist. All of the readers utilized the HEAD-US imaging protocol on 5-6 patients each week in their clinic.

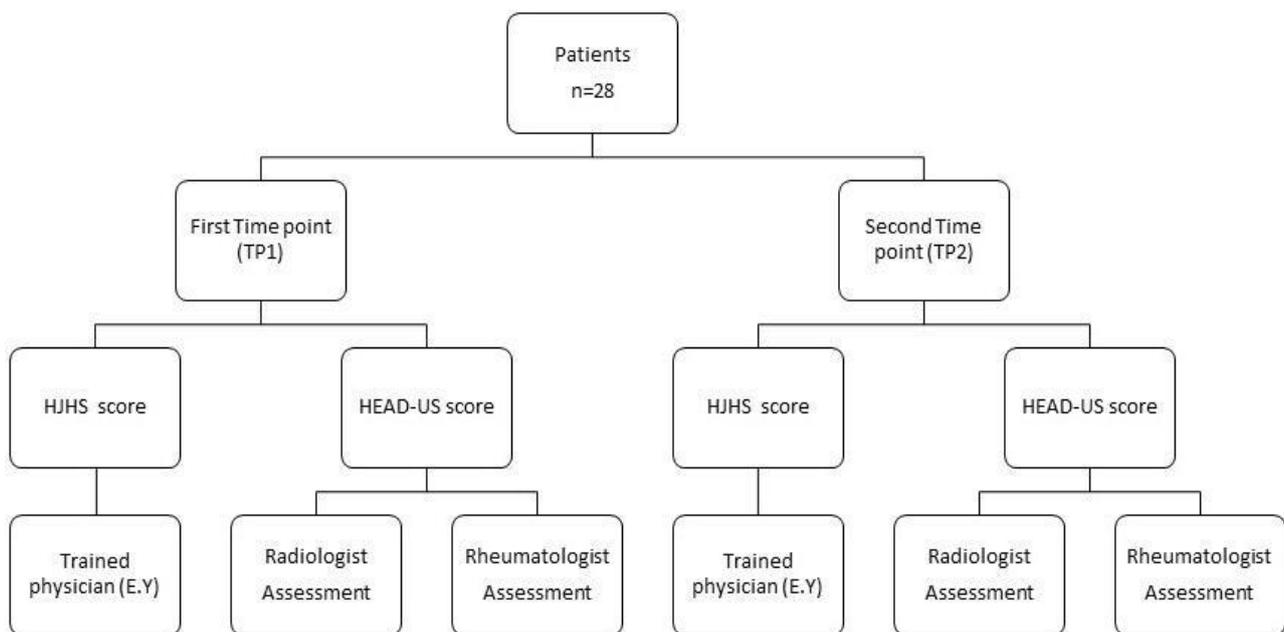


Figure 1: Flow chart of the study protocol in patients with severe hemophilia

HJHS score

The HJHS is a well-known validated physical examination tool that is used to numerically score the joint health and function of hemophilia patients (2). Swelling, duration of swelling, muscle atrophy, crepitus of motion, extension loss, flexion loss, joint pain, strength, and gait are among the nine impairment items in the HJHS. The HJHS were performed by a trained physician (EY) and assessed at six joints (elbows, knees, and ankles). Each item on the HJHS score was assigned a score, which included inflammation (0-3), duration of inflammation (0-1), atrophy (0-2), crepitus (0-2), range of motion (flexion 0-3, extension 0-3), muscle strength (0-4) and pain (0-2), for a total score ranging from 0 to 20 per joint. The gait category received a separate score (0-4). A higher total score indicates poor joint health (2).

HEAD-US

Martinolli et al. developed HEAD-US, a simplified and objective scoring system for hemophilic arthropathy, in 2013 (4). The HEAD-US is sensitive for detecting joint abnormalities, including synovitis, cartilage, and bone damage. The maximum score for each joint is eight points. The score for synovitis is 0 for no or minimal synovitis, 1 for mild or moderate synovitis, and 2 for severe synovitis; for cartilage, the score is 0 for normal cartilage, 1 for partial/complete loss of cartilage thickness affecting 50% of the joint surface, and 4 for total loss of cartilage thickness. The score for subchondral bone is 0 for normal subchondral bone, 1 for mild abnormalities with or without incipient periarticular osteophytes, and 2 for unstructured subchondral bone with or without erosions and obvious periarticular osteophytes. As a result, each joint could be given a score ranging from 0 to 8, with higher scores indicating severe abnormalities. The US machine (GELOGIQ P9TM) with an 8-12 MHz linear probe was used.

Statistical analysis

For statistical analysis, SPSS 15.0 was used. HEAD-US and HJHS were compared using the Mann-Whitney U test. Spearman's correlation coefficients were less than 0.2, 0.2-0.4 weak, 0.4-0.6 Moderate, 0.6-0.8 good, and >0.8 strong. Ki Kare test was used for categorical variables. A $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the 28 patients in the study. There were 23 (82%) with severe hemophilia A and 5 (18%) with severe hemophilia B. The patients were all boys, with a median age of 16 years (range, 6-22 years). Four patients (14%) had inhibitors. Primary prophylaxis was given to 18 (64%) of the 28 patients, while secondary prophylaxis was given to only 10 (36%) of them. The target joint was found in 25 (90%) of the 28 patients and

the remaining 3 patients (10%) were not identified. The target joints were as follows: right ankle (28%), right knee (26%), right elbow (14%), left knee (12%), left ankle (4%), left elbow (4%), and left shoulder (2%).

Table 1: Demographic data

Number of patients	28
Median age (IQR)	16 (6-22)
Type of severe hemophilia	
A	23 (82%)
B	5 (18%)
Inhibitor status	4 (14%)
Prophylaxis status	
Primary prophylaxis	18 (64%)
Secondary prophylaxis	10 (36%)
HJHS score ≥ 1	
TP1	19/28 (68%)
TP2	14/28 (50%)
HEAD-US score ≥ 1	
Radiologist assessment	
TP1	21/28 (76%)
TP2	23/28 (72%)
Rheumatologist assessment	
TP1	24/28 (86%)
TP2	23/28 (82%)

TP: Time point, TP1: 0. Months, TP2: 6. Months, HEAD-US: Hemophilia early arthropathy detection with ultrasound, HJHS: Hemophilia joint health score

HEAD-US assessment in the joints with HJHS zero points

The radiologist found bone damage (22%) in the patient's elbow, synovitis (22%) and a bone (12%) damage in the patient's knee, and synovitis (34%), cartilage (12%), and a bone (12%) damages in the patient's ankle using HEAD-US at TP1 in the joints with HJHS zero points. The rheumatologist used HEAD-US in the joints with HJHS zero points and found cartilage (12%) and bone (22%) damage in the patient's elbow, synovitis (56%), cartilage (44%), and bone (56%) damages in the patient's knee and synovitis (34%), cartilage (34%), and bone (22%) damages in the ankle at TP1. The radiologist used HEAD-US in the joints with HJHS zero points and found synovitis (34%), cartilage (12%), and bone (12%) damage in the patient's knee and synovitis (34%), cartilage (22%), and bone (22%) damages in the ankle at TP2. The rheumatologist used HEAD-US in the joints with HJHS zero points and found synovitis (22%), cartilage (12%), and bone (34%) damage in the patient's elbow and synovitis (44%), cartilage (34%), and bone (34%) damages in the knee and synovitis (22%), cartilage (22%), and bone (12%) damages in the ankle at TP2 (Table 2).

Table 2: HEAD-US assessment of hemophilic arthropathy by different caregivers based on HJHS score

HEAD US	HJHS score 0	HJHS score 0
Radiologist at TP1		Rheumatologist at TP1
Elbow		Elbow
Synovitis score 0≥1, n(%)	9(100%)/0(0%)	Synovitis score 0≥1, n(%)
Cartilage score 0≥1, n(%)	9(100%)/0(0%)	Cartilage score 0≥1, n(%)
Bone score 0≥1, n(%)	7(78%)/2(22%)	Bone score 0≥1, n(%)
Knee		Knee
Synovitis score 0≥1, n(%)	7(78%)/2(22%)	Synovitis score 0≥1, n(%)
Cartilage score 0≥1, n(%)	9(100%)/0(0%)	Cartilage score 0≥1, n(%)
Bone score 0≥1, n(%)	8(88%)/1(12%)	Bone score 0≥1, n(%)
Ankle		Ankle
Synovitis score 0≥1, n(%)	6(66%)/3(34%)	Synovitis score 0≥1, n(%)
Cartilage score 0≥1, n(%)	8(88%)/1(12%)	Cartilage score 0≥1, n(%)
Bone score 0≥1, n(%)	8(88%)/1(12%)	Bone score 0≥1, n(%)
Radiologist at TP2		Rheumatologist at TP2
Elbow		Elbow
Synovitis score 0≥1, n(%)	9(100%)/0(0%)	Synovitis score 0≥1, n(%)
Cartilage score 0≥1, n(%)	9(100%)/0(0%)	Cartilage score 0≥1, n(%)
Bone score 0≥1, n(%)	9(100%)/0(0%)	Bone score 0≥1, n(%)
Knee		Knee
Synovitis score 0≥1, n(%)	6(66%)/3(34%)	Synovitis score 0≥1, n(%)
Cartilage score 0≥1, n(%)	8(88%)/1(12%)	Cartilage score 0≥1, n(%)
Bone score 0≥1, n(%)	8(88%)/1(12%)	Bone score 0≥1, n(%)
Ankle		Ankle
Synovitis score 0≥1, n(%)	6(66%)/3(34%)	Synovitis score 0≥1, n(%)
Cartilage score 0≥1, n(%)	7(78%)/2(22%)	Cartilage score 0≥1, n(%)
Bone score 0≥1, n(%)	7(78%)/2(22%)	Bone score 0≥1, n(%)

TP:Time point, TP1:0. Months, TP2:6. Months, HEAD-US: Hemophilia early arthropathy detection with ultrasound, HJHS: Hemophilia joint health score

Correlation between HEAD-US and HJHS scores

There was a moderate correlation between cartilage and bone damages in HEAD-US and a positive HJHS score in the ankle joints, and a good correlation between synovitis, cartilage, and bone damages in HEAD-US and a positive HJHS score in the elbow joints at TP1 assessment by a radiologist. There was a moderate correlation between synovitis and cartilage damages in HEAD-US and a positive HJHS score in the knee joints and a weak correlation between synovitis in HEAD-US

and a positive HJHS score in the ankle joints and a moderate correlation between synovitis, cartilage, and bone damages in HEAD-US and a positive HJHS score in the elbow joints at TP1 assessment by a rheumatologist. There was a moderate to good correlation between cartilage and bone damages in HEAD-US, and a positive HJHS score in the knee joints, as well as synovitis and cartilage damages in HEAD-US and a positive HJHS score in the elbow joints, at TP2 assessment by a radiologist. There was a weak to good

correlation between synovitis, cartilage, and bone abnormalities in HEAD-US and a positive HJHS score in the knee joints and a moderate correlation between synovitis, cartilage, and bone damages in HEAD-US

and a positive HJHS score in the elbow joints at TP2 assessment by a rheumatologist (Table 3).

Table 3: HEAD-US and HJHS score correlation at two-time points

HJHS score	HEAD-US Radiologist	Synovitic	Cartilage damage	Bone damage	HEAD-US Rheumatologist	Synovitic	Cartilage damage	Bone damage
Knee	TP1	0.35	0.21	0.10	TP1	0.48*	0.45*	0.23
		right	0.35	0.44*		0.12	0.38*	0.42*
		left	0.17	0.12	0.03	0.40*	0.31	0.27
Ankle	TP1	0.34	0.44*	0.52**	TP1	0.38*	0.17	0.31
		right	0.48*	0.68**		0.60**	0.40*	0.30
		left	0.11	0.50**	0.31	0.28	0.39*	0.48*
Elbow	TP1	0.72*	0.78**	0.66**	TP1	0.60**	0.46*	0.40*
		right	0.80**	0.80**		0.72**	0.73**	0.54**
		left	0.10	0.12	0.02	0.01	0.10	0.01
Knee	TP2	0.22	0.57**	0.64**	TP2	0.38*	0.78**	0.40*
		right	0.12	0.45*		0.25	0.22	0.36
		left	0.25	0.70*	0.64**	0.51*	0.65**	0.41*
Ankle	TP2	0.12	0.20	0.36	TP2	0.10	0.24	0.32
		right	0.26	0.32		0.42*	0.18	0.25
		left	0.12	0.01	0.01	0.01	0.45*	0.19
Elbow	TP2	0.58**	0.62**	0.29	TP2	0.43*	0.53**	0.42*
		right	0.56*	0.56*		0.28	0.50*	0.37
		left	0.31	0.38*	0.35	0.14	0.44*	0.07

TP: Time point, TP1: 0. Months, TP2: 6. Months, HEAD-US: Hemophilia early arthropathy detection with ultrasound, HJHS: Haemophilia joint health score, *p<0.05, **p<0.01

DISCUSSION

Several recent studies have reported the early detection of hemophilic arthropathy using HEAD-US in hemophilia patients with an HJHS score of 0 (1,8-11). A comprehensive study found that, except for the ankle joint, lifetime joint bleeding was strongly correlated with the HJHS score (9). HEAD-US was used in a Spanish study to detect subclinical hemophilic arthropathy in at least one joint in 14% of 167 asymptomatic hemophilia patients with an HJHS score of 0. The patient's mean age was 24 years, and 66% of them had severe hemophilia; 30% received primary prophylaxis. The right ankle was the most severely affected joint (10). Another research reveals that 60.9% of hemophilia patients with an HJHS score of 0 had a history of joint bleeding in severe hemophilia. Subclinical hemophilic arthropathies using HEAD-US were found in 4.7% of patients' elbows, 5.7% of knees, and 16.8% of ankles with an HJHS score of 0. All hemophilic patients were children receiving prophylaxis (8). Subclinical hemophilic arthropathy in HEAD-US was found in 5% of patients with moderate hemophilia whose HJHS score was 0 in a multicenter cross-sectional study in Norway (11). In our study, radiologists used HEAD-US to detect 12% to 34% hemophilic arthropathy in patients with HJHS scores of 0 at two different time points. However, in hemophilic patients with HJHS scores of 0, rheumatologists

detected 12% to 56% hemophilic arthropathy using HEAD-US at two different time points. We hypothesized that the high rate of hemophilic arthropathy detected by HEAD-US in patients with HJHS scores of 0 may be related to the patient's age and disease severity. All patients in our study had severe hemophilia and included both young adults and children.

Many studies have been conducted to investigate the relationship between the HJHS and the HEAD-US scores in hemophilia patients (12-16). The researchers have found a moderate correlation between the HJHS score and the osteochondral component of the US score (r=0.45), but a poor correlation between the HJHS score and the soft tissue component of the US score (r=0.26) in a study of 51 children with severe hemophilia/von Willebrand disease (12). An Italian study found a significant correlation (r=0.717) between HEAD-US and HJHS scores in 66 adult hemophilia patients over the age of 16 (13). A Turkish study found a strong correlation (r=0.847) between HEAD-US and HJHS scores in both pediatric and adult hemophilia patients (14). In 70 patients with hemophilia aged 14-33 years, a similar strong correlation (r=0.825) was found between HJHS and HEAD-US score of the knee (15). In a study of 120 children with hemophilia who received on-demand treatment in Indonesia, researchers found a moderate correlation (r=0.65) between HEAD-US and

HJHS scores. The ankle was the most affected joint in HEAD-US, and the knee was the most affected joint in HJHS (16). We found a moderate to good correlation between HJHS score and HEAD-US in 28 hemophilia patients, particularly in elbow and knee joints. Using HEAD-US, experienced trained rheumatologists found moderate to good results in the assessment of hemophilic arthropathy, similar to the radiologist evaluation.

The main limitation of the study was its small sample size. Another limitation was not evaluated using an MRI simultaneously. A comprehensive investigation of a large number of patients will be required in the future.

In conclusion, our findings show that the HEAD-US score can be used to detect subclinical hemophilic arthropathy in hemophilia patients in joints with HJHS zero-point scores.

Conflict of Interest: The authors have no conflicts of interest to declare.

Researchers' Contribution Rate Statement: Concept/Design: EY, ZK; Analysis/Interpretation: EY, ZK; Data Collection: EY, ZK, HS, MY, SK, UK; Writer: EY, ZK; Critical Review: EY, ZK; Approver: EY, ZK
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